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S19 Mitochondrial Gene Expression

19P1

Gene regulation of cytochrome c oxidase subunit 4 isoform 2: A tale of three factors

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Cytochrome *c* oxidase (*COX*) is the terminal enzyme of the electron transport chain, made up of 13 subunits encoded both in mitochondrial as well as in nuclear DNA. Subunit 4 (COX4), a key regulatory subunit, exists as two isoforms, the ubiquitous isoform 1 and the predominantly lung specific isoform 2 (*COX4I2*). We have previously identified a highly conserved 13-bp sequence in the proximal promoter region of *COX4I2* that functions as an oxygen responsive element (ORE), maximally active at an oxygen concentration of 4% [1,2]. We also have identified three transcription factors that bind this conserved ORE, namely RBPJk, CHCHD2, and CXXC5. Interestingly, our data indicate that CHCHD2, an activator of the ORE, has a dual localization in the mitochondria and the nucleus, possibly with distinct functions. To validate the results derived from cultured cells, we show using RNA interference the role of these transcription factors in the gene regulation of *COX4I2* in primary pulmonary artery smooth muscle cells. We present a model proposing that the nuclear CHCHD2 regulates *COX4I2* gene expression and the mitochondrial CHCHD2 regulates COX function. Finally, under hypoxic stress, a concerted action of the three transcription factors enhances the expression of *COX4I2* that in turn could be responsible for the augmentation of both COX activity and its properties to cope with the altered cellular energy requirements.

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19P2

Transcriptional patterns of ATP-synthase subunits in rat liver and muscle tissues during development

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The mitochondrial biogenesis and adequate energy production are important for fetal growth and early postnatal adaptation. The crucial stage of development is the postnatal switch of glycolytic to oxidative metabolism when the full OXPHOS activation has to proceed. The additional knowledge could help to assess mitochondrial dysfunction associated with inefficient activation of OXPHOS. The key enzyme in OXPHOS is F1F0 ATP synthase (complex V) ensuring the production of most of the ATP in mammalian organisms.

The aim of this study was to characterize the expression of complex V subunits — *atp5g2*, *atp5o* and *atp6* (mitochondrially encoded) in liver and muscle tissues during rat development. The changes of mtDNA content were also analyzed.

Material and methods: The gene expression analyzes were performed in set of 105 rat liver and muscle tissue samples collected between the 17th fetal day and the 5th postnatal day. The quantification of mtDNA and mRNA was realized by real-time PCR method.

Results: The marked differences were observed in mRNA levels of ATP synthase subunits between liver and muscle tissues during rat development. The significant positive correlations were found between mRNA levels of *atp5g2, atp6, atp5o* and age ($r = 0.44$, $p < 0.01$; $r = 0.82$, $p < 0.01$; $r = 0.42$, $p < 0.01$) in liver tissue. By contrast in muscle tissue, the *atp5g2* and *atp5o* transcript levels were without significant changes ($r = -0.18$, $p > 0.05$; $r = 0.18$, $p > 0.05$). Indeed, only *atp6* gene was established with similar result in both muscle and liver gene expression analysis (muscle: $r = 0.83$, $p < 0.01$). Despite the differences in mRNA levels between tissues, the dendrograms of all transcriptional patterns were similar in both tissues. The mtDNA levels increased in analyzed tissues throughout the period (muscle: $r = 0.62$, $p < 0.01$; liver: $r = 0.75$, $p < 0.01$).

Conclusions: Our study confirmed that *atp5o* and *atp5g2* belong to low transcript gene group (LTG). Their transcript levels were from tenfold to thousandfold lower in comparison with *atp6* transcript level in analyzed rat tissues. We described the similar increasing mRNA level of mitochondrially encoded subunit (*atp6)* and mtDNA level in two different rat tissues. Moreover on the basis of the results we find the specific expression breakpoint during development which should be studied in more details.

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